The Communication of Secondary Variants:

Interviews with Parents whose Children have Undergone Array-CGH Testing

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Conflict of Interest Statement

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Abstract

Children with unexplained developmental disabilities or congenital anomalies are increasingly being referred for genetic diagnostic testing using array-comparative genomic hybridisation (array-CGH) and next-generation sequencing (NGS) technologies. Their parents will have to deal with the secondary variants that will inevitably arise. We conducted 16 prospective semi-structured interviews with native Dutch-speaking parents whose children had undergone clinical array-CGH testing. The interviews explored the parents' experiences, expectations and opinions, specifically regarding the communication of results. Concrete examples of "unexpected results" were provided to help guide the discussion, differing in severity, treatability, time of onset, level of risk, and carrier status. Data was analysed using content and narrative analysis methodologies. Parental motivations for and against the disclosure of unexpected results cluster around four main themes: actionability; knowledge; context; and characteristics of the result. Most parents wished to know all types of results. Disclosure was framed within a holistic, contextual, family-wide view. Genetic counselling should aim to integrate explorations of the motivations of parents surrounding the disclosure of results with good clinical care.

Keywords

disclosure; ethics; genetics; incidental findings; patient preferences

Introduction

Array-comparative genomic hybridisation (array-CGH) is currently the preferred genetic diagnostic test for individuals with unexplained developmental disabilities or congenital anomalies. (1) Array-CGH and next-generation sequencing (NGS) technologies mark a paradigm shift in terms of the amount of genetic data produced and the bioinformatics and other support needed to maximally utilise and interpret this data. (2) The shift away from focussed genetic testing also effects a paradigm shift in clinical settings.

One of the most pressing questions in the application of these novel technologies in clinical genetics settings is what to do with the secondary variants (also known as incidental findings) that will inevitably arise. (3-5) An increasing amount of empirical research is being devoted to this topic. (6) This includes the views of patients or their parents. (7-10) As the recipients of genetic test results potentially including secondary variants, it is vital that their voices be heard.

We interviewed native Dutch-speaking parents whose children had undergone array-CGH testing for a diagnosis for their developmental delay with or without dysmorphism or congenital anomalies. The interviews covered the experiences, expectations and opinions of parents, specifically regarding the communication of results. The term “unexpected result” was used. Although we prefer to use “secondary variants” in professional discussions, (11) we found “unexpected result” to be a term that parents could more easily understand in interviews. ”Unexpected result” was defined to parents as something which the doctor might hypothetically coincidentally find, and distinguished from the “expected result”, a diagnosis or explanation for the current clinical condition of their child. This article focuses on what motivates parents to want to know or not know secondary variants.

Materials and methods

Participants

Semi-structured interviews were conducted in Dutch with parents whose children had undergone clinical array-CGH testing. None of the parents had received secondary variants. The testing had to have been completed and all results (including "no result") known by the parents; in this way, the discussions on secondary variants were completely hypothetical, against a background of experience with the return of genetic results. The children had to be under the age of 6 years at the time of interview, to ensure that genetic testing was a recent memory for the interviewees.

Recruitment was conducted in cooperation with staff of the genetics centre at a single Belgian university hospital (co-authors KDV, HP and HVE). Interviews were conducted at home, at a time that best suited interviewees. No compensation was offered. Preference was given to couple interviews to allow the generation of more comprehensive data and the co-construction of meaning during the interview. (12) When it was not possible to interview both parents, the absent parent was warmly encouraged to contact the interviewer if they wished to add anything to their partner's answers.

Data collection and analysis

The interview guide was developed by three authors (GC, KDV, KD) on the basis of two systematic reviews conducted previously and clinical experience. (6, 13) The first part of the interview focussed on interviewees' experiences with genetic testing. The second part concerned a discussion of secondary variants. The interviewer explicitly emphasised the coincidental or accidental nature of secondary variants and the hypothetical nature of the discussion in the case of the interviewees and their child. The disclosure of a series of examples of secondary variants was discussed (Figure 1). Examples were chosen to represent the wide variety of results possible from the new genetic paradigm, (14) not necessarily from array-CGH testing. Interviewees were instructed that such secondary variants could be found by new types of genetic testing "such as array-CGH." A general

discussion of secondary variants followed. The third and final part of the interview discussed the possible recontacting of the couple if a primary result or secondary variant were discovered years later. For more details, see the supplementary online material.

The interviews were recorded on tape following consent. Transcripts were analysed using NVivo 9 software and content and narrative analysis methodologies. (15-17) The accuracy and applicability of codes developed by the interviewer (GC) were checked for one representative interview by two co-authors (KDV, KD), and consensus reached. The current article focuses on the personal motivations spontaneously provided by interviewees surrounding the disclosure of secondary variants. Unless otherwise stated, specific motivations were only raised by a random, nondistinctive subsection of parents.

Results

Study population

Recruitment took place between March 2012 and June 2013. A total of 26 couples were contacted, and 16 interviews were conducted (response rate 62%). While coincidentally none of the couples who declined to participate had received a diagnosis through genetic testing, only one explicitly gave this as a reason for not participating. Other reasons included lack of time, lack of interest and that an interview would be “too confrontational”. The interview guide was not substantially altered after any of the interviews. Initial analysis suggested thematic saturation after ten interviews, which the six additional interviews confirmed. Due to the father’s work commitments, three interviews were conducted with the mother alone, and one interview was conducted with the mother and her mother-in-law (only the mother’s answers were included for analysis). Interviews lasted approximately 2 hours (range: 60-162 minutes).

All of the couples experienced a high degree of uncertainty about the future of their affected child, whether or not array-CGH testing had resulted in a diagnosis - understood as a causal genetic mutation, previously identified in other cases. This uncertainty was often coupled with loneliness, and

stemmed from the fact that their child had a "genetic condition." All but two of the affected children were moderately to severely physically and mentally disabled. Table 1 provides various details about the children and their parents.

When discussing their experiences with genetic testing and how they would respond to the disclosure of secondary variants, it was evident that all couples felt supported by their families and genetics centre staff. General satisfaction with genetics centre staff was illustrated for instance in discussions about the preferred manner of disclosure. All interviewees answered that they would prefer hearing about secondary variants in a face-to-face conversation with their geneticist, especially if the secondary variant was considered to be "bad news". Reasons given included participants' confidence in the geneticist to disclose in a "human" way, open to and able to respond to questions about the secondary variant.

Motivations surrounding the disclosure of secondary variants

Figure 2 divides the disclosure preferences of parents according to example. Such a graph, only displaying the final answers of parents, masks all the discussions and disagreements that took place. Some participants changed their position as a result of their own or their partner's arguments, while others became more entrenched in their original position. Most found the questions "difficult". Many openly acknowledged that they seemed to be contradicting themselves. Some opinions and motivations were more strongly stated than others.

The motivations provided by parents supporting their desire to receive secondary variants can be grouped around four main themes (Table 2). The themes overlap to some extent, and received different emphases depending on the particular example (Table 3).

Actionability

The most important group of motivations was actionability; it was always cited in discussions of example 1 and returned to in the general discussion at the end. Sometimes discussions on actionability would turn to possible prenatal choices. Parents would then often openly acknowledge

the apparent paradox of loving their specific disabled child very much and still wishing to have the choice to avoid other serious sickness like Duchenne muscular dystrophy (example 2); life was difficult enough with one sick child. Some also emphasised the difference between having a hypothetical discussion and actually being faced with a concrete, difficult prenatal decision.

Knowledge

A second theme was knowledge. Some parents said they "just want[ed] to know everything", and were consistent across all examples in favouring disclosure. Others "just want[ed] to know" specific examples, and had difficulty explaining why. The motivation of knowing what will happen in the future, and the conviction that a given example would impact the future, were cited as motivators by various interviewees across all examples. However, the image of a crystal ball was often used to put this into perspective: much as some parents might want a "crystal ball" to look into the future, they acknowledged that this was unrealistic and possibly undesirable. Additionally, almost all parents made a distinction between their interest in secondary variants and targeted findings; when asked if they would like the doctor to specifically go looking for particular "secondary variants", almost all said it was unnecessary unless the doctor had some reason to suspect the secondary variant based on symptoms or family history. The fact that a test had been carried out and a result found was a reason for disclosure; it was clear from the way in which interviewees talked about such a finding that they understood that it would only turn up coincidentally, and would not be specifically sought for. The theme of knowledge also included sharing the knowledge. For example, most found it unacceptable if the doctor would know something and not disclose; this included some who said that they would rather the doctor disclose something against their stated will, than that the doctor would know a certain unexpected result and not disclose. Some said that if the secondary variant were found in one child, they would of course want to know about the other children too. All wanted to share the information with other family members if the latter were open. Some made a distinction between knowing and then acting on the knowledge, and valued having the choice to know. Knowledge of

secondary variants was also appreciated as a way to avoid reproaches or regrets retrospectively. There was some concern that the knowledge might get lost if not disclosed immediately to parents.

Context

A third theme was the context of interviewees, expressed in two main ways: secondary variants should be disclosed because of existing relationships with geneticists, the world of genetics, and the wider family, that foster expectations of disclosure; secondary variants should be disclosed because they already have a disabled child requiring so much careful planning and are caught up in the genetic testing treadmill. The idea of the duty or responsibility that parents owe to their children, as motivation for wanting to know secondary variants, was framed in the context of parent-child relationships, and was cited by various participants across all examples. A related contextual argument was "because it's something about *my* child", and a few participants said they would be more likely to want disclosure for their child than for themselves.

Secondary Variant Characteristics

A final group of motivations, mainly mentioned in the general discussions at the end of each interview, involved specific characteristics of the secondary variant, such as its seriousness and the certainty of developing symptoms.

The motivations provided by parents supporting their wish not to receive secondary variants were more example-specific (Table 3). As everyone wanted to know a secondary variant related to child cancer (Figure 2), no motivations not to know were given for example 1. In general, motivations against disclosure were the antithesis of the four themes of motivations favouring disclosure (Table 2): if the actionability of the secondary variant was in doubt; if it was feared that the knowledge may have negative consequences, for instance on the ability of the child to "just be a child"; if the context

of interviewees decreased the importance of the secondary variant; and specific characteristics of the secondary variant including its non-immediacy.

A few motivations were spontaneously mentioned only by a certain type of parent. It must be emphasised that as no parents were explicitly asked about a motivation, it cannot be said that these motivations only meant something to parents of a particular type or no parents of the opposite type. Only parents who had not (yet) received a diagnosis for their child stated that they would like to know so as to not live in ignorance or to understand what has happened once the condition manifested, for future children, or if the result was "certain". Regarding motivations against disclosure, only parents who as yet only had one child reasoned that they would not need to know about carrier status because their affected child will never have their own children; conversely, only parents who had other, healthy children said that they would not need to know about late-onset conditions (specifically examples 3 and 4) because the child could ask themselves when they reached majority.

Discussion

The desire of all parents to want to know a serious and treatable secondary variant that affects children and will definitely appear, as in the case of example one, matches recommendations that parents not be given the choice to refuse such a secondary variant. (18) However, the interest of the majority of parents in other types of secondary variants runs counter to recommendations that only serious, clinically actionable findings be disclosed. (19) Participants' predicted responses to certain types of secondary variants are also in conflict with research on the variable uptake of predictive testing for late-onset familial conditions or the real impact on behaviour after genetic risk testing. (20-22) The expectations and views of parents and patients, empirical research on genetic testing, professional expertise and evolving guidelines all form complementary facets of research and clinical practice.

Interviewees had a rich understanding of both "serious" and "actionable". Similar to the views of lay participants in other qualitative research, the clinical relevance of a secondary variant was not

sufficient as the sole standard for disclosure. (10) Interestingly, the negative emotional responses often listed as potential harms of disclosure seldom mentioned in interviews, or participants were more inclined to acknowledge that while it would be difficult to hear such a result they still favoured disclosure. The direct experiences of interviewees increase the reliability of their predicted emotional responses. (23) Furthermore, interviewees considered secondary variants to be something which belonged to the whole family, as evidenced by the way in which they discussed the implications of examples 3 and 5 and their willingness to share genetic information with the extended family. Support for viewing secondary variants of adult-onset conditions in children as family matters can be found in some of the recent clinical literature, (24, 25) and is in line with earlier research on the attitudes of parents towards testing their children's cystic fibrosis carrier status. (26) The idea that wider family implications might be a reason for caution in disclosure, suggested by some authors, (13) was not a concern. Those who had difficulties with some family members said they would just not disclose to them; it did not occur to them that this might be a reason to forgo disclosure altogether.

The involvement of children in the scenarios was more often an encouragement to want disclosure than a deterrent. This may be because most of these children will always be very dependent on their parents or other caregivers. It could be said that parents saw themselves as the "gatekeepers" of information for their children. (8) The "respect for the open future of the child" concept, so lauded in the literature, (27) did not appear to be part of the interviewees' lives or ways of thinking. It is noteworthy that only parents who had other, healthy children said that they would not need to know about late-onset conditions because their future adult child could ask themselves; it was as if the other parents whose only experience of children was disability could not so readily imagine independent grownup children. Parents often referred to their specific context of caring for a disabled child as a reason to want to know secondary variants, also remarking that they could imagine that parents of healthy children, who do not have to plan their lives around their child's disability, might be less inclined to want to know secondary variants. The specificity of interviewees is a limitation of this study. It means that the results may not be generalisable to parents in general. However, parents with disabled children will continue to be the first recipients of NGS.

Our research complements and extends similar research recently published by Sapp *et al*. (9) The current study goes further in including more scenarios, which allowed more motivations to surface. We report comparable results for Sapp *et al*.'s first two secondary variant scenarios (examples 1 and 3 here), although a higher degree of interest in carrier status. The reason for this discrepancy is unclear, possibly related to cultural differences or the high level of public awareness of recessive conditions (Table 3, example 5). Future research could investigate the motivations of those who have experience receiving secondary variants.

One limitation of the current study is that 80% of the couples were recruited through a university hospital. Interviewees thus represent only a certain clinical population. Study participants were generally highly educated and articulate, as is common in interview research. Moreover, given that array-CGH testing only provides a diagnosis in up to 17% of cases of unexplained intellectual disability, (31) it is unfortunate that a greater proportion of those who have not (yet) received a diagnosis did not participate. While it is not possible to discover all of the examples of secondary variants discussed in the interviews using array-CGH, the focus of the study was to explore hypothetical scenarios made possible by the new genetic testing paradigm, of which array-CGH is an example.

Sometimes the motivations suggested supporting disclosure were based on inaccurate medical knowledge or an overestimation of either the usefulness of the information or its impact on behaviour. Counselling should address this. (32) However, counselling discussions should also bear in mind that "usefulness" can mean different things to different people. Discussion of the motivations of parents and patients, framed within their holistic, contextual view of genetic testing, should be brought together with good clinical care. (33) The parents included in this interview study all showed a high degree of trust in the scientific and clinical expertise of their geneticists. Such trust is a necessary basis for making complex disclosure decisions about genetic secondary variants, and must be continually striven for.

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Figure and table titles and legends

Figure 1: Examples of secondary variants provided in the interviews for discussion.

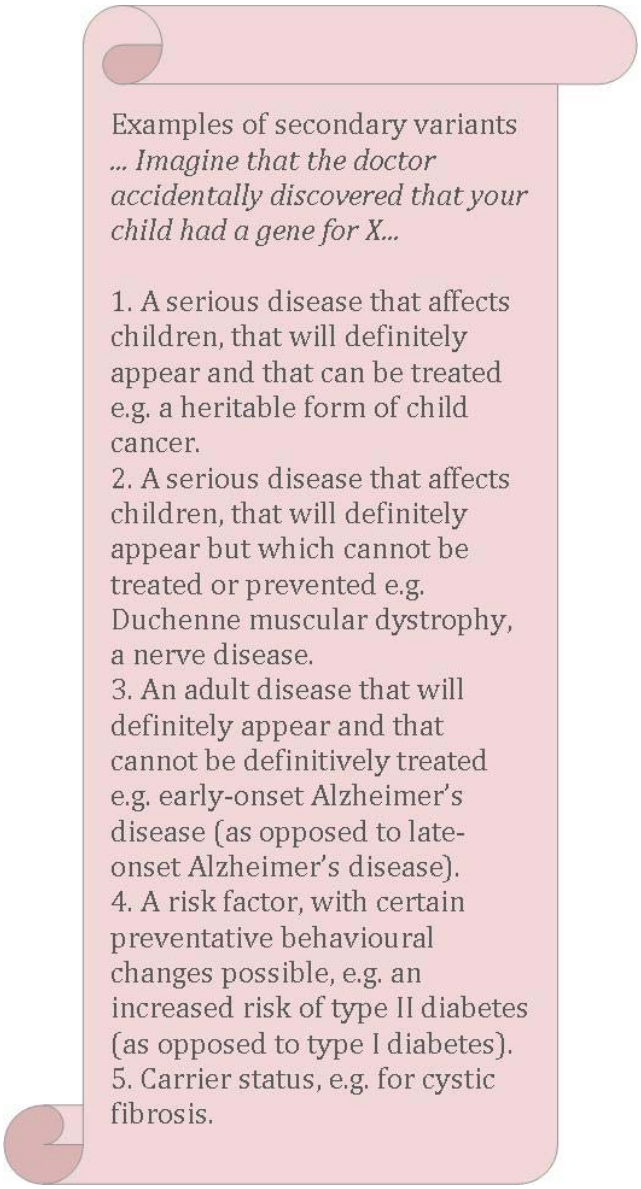

Figure 2: "Imagine that the doctor accidentally discovered that your child had a gene for X... would you want to know?" Some parents changed their minds in the course of the discussion; only their final answer (yes, maybe, no) has been counted here.

Legend for Figure 2: ■ No ■ Unsure ■ Yes

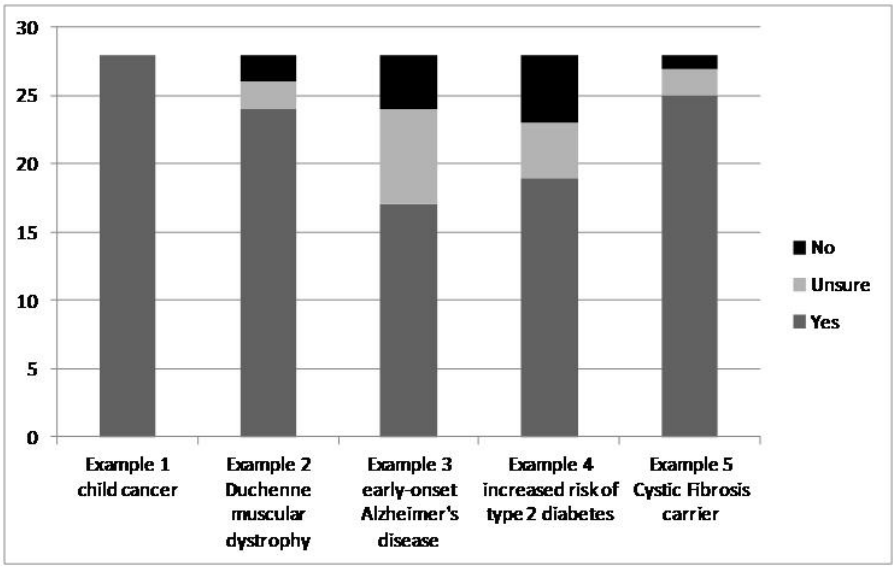

Table 1: Socio-demographic details for the interviewees and their children, plus some details on their genetic testing experiences.

	Father	Mother
Information about the parents		
Age		
25-34	5	9
35-44	10	7
45-54	1	0
Highest study level		
Secondary education	7	4
Non-academic tertiary education	5	7
University tertiary education	4	5
Information about the child		
Gender of child		
Male	6	
Female	10	
Age of child at first genetics centre visit		
< 6 months	6	
6 months < child < 1 year	3	
1 year < child < 2 years	3	
2 years < child < 3 years	4	
Position of child in family		
First child	6	
Second child	5	
Third child	5	
Miscellaneous		
Time between receiving array-CGH result and interview		
< 6 months	8	
6 months < x < 1 year	5	
1 year < x < 2 years	2	
> 3 years	1	
Number of genetics centre visits (before interview)		
2 visits	6	
3 visits	6	
4 visits	4	

Table 2: Motivations raised in the interviews surrounding the disclosure of secondary variants.

Theme	Pro-disclosure	Anti-disclosure
Actionability	Treatment	Doubtful actionability
	Prevention	
	Preparation	
Knowledge	Just want to know (everything)	Possible negative consequences
	The future	
	Already been found	
	Sharing knowledge	
	To have choices	
	No regrets/reproaches	
Context	Existing relationships foster disclosure expectations	Decreased importance of the secondary variant because of the context
	Personal context	
Secondary variant characteristics	Seriousness	Not so serious
	Certainty of developing	Not a certainty
		Non-immediacy

Table 3: Motivations raised per example surrounding the disclosure of secondary variants, with representative quotations. Interviewees are identified as mother/father, gender and age of affected child, and whether or not they have received a diagnosis through array-CGH testing (d+/d- respectively). Quotations have been translated from Dutch by the bilingual interviewer.

Secondary Variant Example	Motivations supporting disclosure	Representative Quotation	Motivations against disclosure	Representative Quotation
Example 1: A serious disease that affects children, that will definitely appear and that can be treated e.g. a heritable form of child cancer	Actionability to save their child's life; to implement earlier screening; to recognise the symptoms on time; possibly make reproductive choices; to test themselves and their other children if appropriate; pass on the information to other family members; disclosure would give time to prepare, so that the couple would know what would happen or could imagine the future and make plans appropriately; doctors have a duty to disclose based on the result's actionability Knowledge so that there would be no unanswered questions or regrets afterwards; something you "have" to know; right as a parent to know Context doctors have a duty to disclose based on the doctor-patient (/parent) relationship; the example was recognised as something serious and difficult that would impact the future, but two interviewees discussed how they knew they could handle disclosure based on how they handled their current situation	*Of course [I'd want to know]. Me anyway. And certainly if it can be treated, that there's something you can do, yes. Yeah, I wouldn't know why anyone [wouldn't want to know]... (mother, girl 3 years, d+)*	(none given)	(n/a)
Example 2: A serious disease that affects children, that will definitely appear but which cannot be treated or prevented e.g. Duchenne muscular dystrophy, a nerve disease	Actionability palliative care; possible reproductive choices for the couple or their other children if applicable; some wanted to know this example more than example 1 precisely because nothing could be done; disclosure would allow them to be on time, e.g. in recognising the symptoms, or would give them time; emphasis on practical and mental preparations, e.g. house renovations and acceptance of the inevitable Knowledge know now to be ready for when prevention or treatment would be possible; to avoid the regret of not treating the child appropriately, e.g. to not interpret as "misbehaviour" what is part of the illness, or to be able to give the sick child the help they need; to make the most of the time remaining; so that the information would not get lost; knowledge would allow the couple to make choices; duty of the doctor to disclose Secondary variant characteristics the inevitability of the appearance of symptoms	*... to be prepared to... "mourn" is a big word <laugh> but I mean also maybe the right word, more to learn to live with it... to process it, to be given the time or something to process the sickness that your child has, that's why, I think, you know? (father, girl 4 years, d-)*	Actionability question of what to do with the "extra" time if the doctor were to disclose now; given that there is nothing that can effectively be done in terms of treatment or prevention, the couple might just spend the time worrying or depressed, which would have an unwanted negative effect on the children Knowledge sometimes it is just better not to know; unrealistic to think that knowing now would enable one to make the most of the time remaining; if the medical experts advised against it Secondary variant characteristics the inevitability of the appearance of symptoms without being able to do anything; if it was going to happen anyway, the couple could just wait	*But you could also say, "If you know it, then you will live more consciously and that will increase your quality of life. (mother, boy 4 years, d+)* *I think that will be of short duration. (father)*
Example 3: An adult disease that will definitely appear and that cannot be definitively treated e.g. early-onset Alzheimer's disease (as opposed to late-onset Alzheimer's	Actionability earlier screening; concern that the symptoms of early-onset Alzheimer's disease could easily go unrecognised; need to prepare the child's environment in cases where the child would always need specialised care anyway due to their disabilities; good to be given the time to learn how to cope with someone with Alzheimer's disease; participants would regret not being given the chance to plan their lives accordingly; knowing would motivate them to improve their quality of life, and they would encourage their child to live differently Knowledge parents would need to know this secondary variant about their child in order to get themselves tested; the only scenario where one parent used the phrase "right of the child to know"; in order to have a realistic image of the child's future; "the more you know the better"; "why not [know]?"	*... That you know it, because by the time that the doctors have actually done all the tests so they know what it is, but if you already know "that'll be the cause", you can win lots of time and know how to cope... ... Maybe you could take a course about "how to cope with a 40 year old with Alzheimer's." It's true, you know? That can take away lots of frustrations, I think. (mother, girl 3 years, d+)*	Actionability question of what to do with the "extra" time if the doctor were to disclose now; concern of negatively impacting the child's adult future, possibly through insurance coverage disadvantages; those who believed the symptoms would be easily recognisable did not have to know Knowledge concern that the knowledge might rob their child of opportunities they would otherwise have taken, which would then be a source of regret	*But then that child will maybe never get married, never have children. He'll always have that... as a family you'll always have that in the back of your head. You might rob him of opportunities, I think. (mother, boy 2 years, d-)*

onset Alzheimer's disease)	Context most of the interviewees were under the age of 40 (average age: 36), and this example was introduced as becoming relevant around that age, so the personal relevance of the example was readily apparent; the context was seen as the whole family, as the result would be important to the whole family; also, parents should be told now so that they could tell their children when the time came (though there was much discussion about how and when disclosure to the child should take place), and so that the parents would be able to look for support from the wider family		Secondary variant characteristics non-life threatening, non-physical, something that would happen in the distant future	
Example 4: A risk factor, with certain preventative behavioural changes possible, e.g. an increased risk of type II diabetes (as opposed to type I diabetes)	Actionability possible prevention; timely recognition; management of symptoms; many were convinced both of the actionability of this secondary variant and its impact on their lifestyle and behaviour Knowledge know now to allow the choice to change behaviour, and to allow parents to pass on the information to their children, thus giving them the choice too; parents could then get informed about the condition and the latest research; one more piece of possibly useful medical information Context the information would carry more weight if it came from a geneticist rather than a general practitioner; those with a family history of diabetes were interested in the information because they knew the condition's impact; considered to be a condition whose severity is often underestimated	*Of course! There are all sorts of things you can do! (father, boy 1 year, d+)*	Actionability worry that the information might cause parents to over-react, treating their child differently when it may not be necessary or prevention may not be completely reliable; scepticism that knowing would cause them to change their behaviour drastically - either they were already involved in regular check-ups or healthy eating, or they doubted that the secondary variant would help Context the fact of knowing people, including top sportspeople, who had diabetes and could cope with it; viewed as a common condition; could wait to receive the information from the family doctor before starting prevention; one interviewee (who also had older children besides the affected child) mentioned the fact that symptoms only appear in adulthood, and she might want to know about herself but not about her children Secondary variant characteristics only an increased risk, not a certainty, and this was set against a context of risk information in general	*Plus it is only the chance that you'll get it, right? If you have to start taking into account all the things that you possibly could get, then you might as well never go outside, never go in the sun because then you might get skin cancer, you might as well never do sport because then you might get asthma... I think the main thing is to keep living in a good way. (father, girl 4 years, d-)*
Example 5: carrier of e.g. cystic fibrosis	Actionability to then test partners and other family members for their carrier status; a few who had no plans to have more children still expressed a desire to subsequently test their own carrier status, either just of curiosity or to be able to tell the child later; so that their child and the child's future partner would get the chance to know and be able to explore their reproductive options; to be able to look after the child once they were told the information later Context parents felt it was important for their child to know their carrier status and explore their reproductive options precisely because they knew how difficult it can be with a disabled child; many participants were familiar with cystic fibrosis through friends, colleagues, or recent local media attention in documentaries and films, and viewed the secondary variant as potentially serious information; others saw no harm in knowing because it was "just information" and not as drastic as some of the earlier examples	*... so that at that moment you can say to your child look, voila, you have the choice, keep it in mind, it could happen, get informed, but make your own choice, because I don't think that we as parents have the right to say, you're not allowed to have any children or whatever, I mean, but look, here is the information, go to the geneticist. (mother, girl 3 years, d+)*	Actionability the uncertain likelihood that the secondary variant would have consequences, either because their affected child would never be able to have children of their own, or because it was only a chance that two carriers will meet each other	(All but three interviewees wanted to know this secondary variant)